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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/706,275 | 11/13/2003 | George H. Lowell | 021989-000710US | 5646 |

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| EXAMINER | |
|---|---|
| MINNIFIELD, NITA M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 06/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/706,275 | LOWELL ET AL. | |
| | Examiner | Art Unit | |
| | N. M. Minnifield | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3-10 and 13-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-10 13-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

1. Applicants' amendment filed March 9, 2006 is acknowledged and has been entered. Claims 1, 2, 11 and 12 have been canceled. Claims 3-10 and 13-18 have been amended. New claim 19 has been added. Claims 3-10 and 13-19 are now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment and/or comments with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3-5, 7-10 and 13-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine composition comprising the peptide antigen SEQ ID NO: 2 and a proteosome adjuvant or a vaccine comprising MtsA and a proteosome, does not reasonably provide enablement for a vaccine comprising at least one (i.e. any) group A Streptococcus antigen and a proteosome adjuvant and methods of treatment or prophylaxis of all group A Streptococcal infection in an individual comprising administering a vaccine composition comprising at least one (i.e. any) group A Streptococcus antigen and a proteosome adjuvant to the individual. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is enabled for a J14/proteosome adjuvant composition. The J14 peptide is SEQ ID NO: 2. The examples set forth in the specification teach a J14/proteosome, nJ14/proteosome (J14 amino terminal anchor/proteosome adjuvant) and a cJ14/proteosome (J14 carboxyl terminal anchor/proteosome), as well as various defined ratios of construct components. J14 is a portion of the M protein of Streptococcus pyogenes. The specification is not enabled for the GAS vaccine wherein the antigen is protein H peptide.

The state of the art with regard to vaccines for group A Streptococcal infections is unpredictable. The state of the art indicates that Group A Streptococci (GAS) are among the most common and widespread human pathogens; they cause acute pharyngitis, impetigo, acute rheumatic fever, rheumatic heart disease and acute glomerulonephritis (Hayman et al Immunology and Cell Biology, 2002, 80:178-87; see p. 178). Hayman et al also teaches that protection against GAS infection is believed to be mediated predominantly by opsonic antibodies directed against the surface M protein, the major virulence factor of GAS (p. 178, col. 1). Hayman et al teaches that the "elucidation of protective epitopes within the M protein of GAS has proceeded rapidly, thus permitting the development of the peptide vaccines that could elicit protection whilst avoiding autoimmunity. Unfortunately, the prospects of a useful vaccine have lagged, in part due to the lack of a suitable means of inducing high titer anti-M protein responses when immunizing with synthetic peptides." (p. 178, col. 2) Olive et al (Vaccine, 2002, 20:2816-2825) teaches that GAS infection includes

pharyngitis, impetigo, scarlet fever, toxic shock syndrome, narcotizing fasciitis, rheumatic fever, rheumatic heart disease and throat infections (p. 2816, col. 1). "Current treatment for controlling GAS infection and GAS-associated diseases is with long-term high dose antibiotic therapy (citation omitted). However, this approach is largely inadequate due to poor compliance, highlighting the need for a GAS vaccine to prevent GAS-associated diseases." (p. 2816, col. 2) Although the M protein of GAS appears to be a viable strategy for a GAS vaccine, the "development of a broad-based vaccine against GAS infection has been impeded by the sequence variability that occurs between different GAS M proteins, and the possibility of inducing immune responses that are cross-reactive with cardiac and other host issues. A GAS vaccine candidate based purely on the M protein type-specific determinants is likely to provide protection only against specific GAS strains, and since there are at least 100 different GAS serotypes this approach would no be efficacious." (p. 2817, col. 1; see also Brandt et al, Infection and Immunity, 2000, 68/12:6587-6594) Olive et al (Vaccine, 2005, 23:2298-2303) teaches that the "variability in M proteins and the potential for the induction of autoimmunity due to antigenic molecular mimicry between GAS M protein and self antigens (citation omitted) represents significant hurdles in the development of a broad-strain coverage vaccine. Multivalent M protein constructs containing epitopes from several type-specific regions of different M proteins (citations omitted) and those based on the conserved C-region (citation omitted) have shown promising results in animal trials. However, the efficacy of the GAS vaccine constructs required the use of adjuvants that can cause adverse side effects." (p. 2298)

The state of the art indicates that at the present time there is not a vaccine for GAS infections. Further, the art teaches that only the M protein of GAS has been deemed a possible antigen for a vaccine against GAS infection, not any GAS antigen as now claimed (see claim 1). Even though M protein appears to be a possible vaccine candidate, multiple M proteins from different GAS serotypes are needed in the vaccine to develop a broad-strain coverage vaccine, not one that simply contains one GAS antigen. The current state of the art indicates that the claimed invention is unpredictable with regard to the scope of the claimed invention. The specification does not provide any evidence for the scope of enablement of a vaccine to protect against any GAS infection using at least one of any GAS antigens and a proteosome adjuvant.

Finally, it should be noted that whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art.

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. See MPEP § 2164.05(b).

The state of the prior art provides evidence for the degree of predictability in the art and is related to the amount of direction or guidance needed in the

specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification.

The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date.

35 U.S.C. 112 requires the specification to be enabling only to a person "skilled in the art to which it pertains, or with which it is most nearly connected." In general, the pertinent art should be defined in terms of the problem to be solved rather than in terms of the technology area, industry, trade, etc. for which the invention is used.

The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. > Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application").< Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what

was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).

In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). If individuals of skill in the art state that a particular invention is not possible years after the filing date, which would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Claims not directed to the specific virus and the specific animal were held nonenabled. Such is the case with the instant application.

The rejection is maintained for the reasons of record. Applicant's arguments filed March 9, 2006 have been fully considered but they are not persuasive. Applicants have asserted that the specification enables a person skilled in the art to make and use, readily and without undue experimentation, vaccine compositions comprising a proteosome adjuvant and at least one group A Streptococcal antigen attached to a hydrophobic moiety, wherein the antigen comprises an antigenic peptide between 6 and 25 amino acids in length from the conserved C-terminal region of a group A streptococcal M protein (see, e.g., page 15, lines 1-27). The specification describes that group A streptococcal M proteins have a conserved region in the carboxy terminus that may be useful for inducing an immune response to more than one serotype of *S. pyogenes* without inducing antibodies that may cross-react with human proteins (see, e.g., page 15, lines 1-27: Figure 1). The specification further provides an example of such a peptide (SEQ ID NO: 1) in this conserved carboxy terminal region (see e.g., page 15, lines 1-15) (See Remarks, p. 12) However, claim 3 is only described on the specified pages. The Examiner acknowledges that there is written description, not enablement of the claimed invention as previously set forth above.

Applicants have asserted that the specification teaches a vaccine composition comprising a proteosome adjuvant and a group A streptococcal antigen, wherein the antigen is selected from an MtsA peptide or a protein H peptide. Applicants have asserted that exemplary Mts peptides are described in the specification, and a working example demonstrates the immune response elicited in animals that were immunized with an MtsA peptide (see, e.g., page 15, line 28 through page 16, line 13; page 38, Table 13). With regard to these arguments it is

noted that the specification at pages 15-16 only describes EIN 19 which is the N-terminal region of MtsA and Table 13 on page 38, this does not enable the scope of the claimed invention of any MtsA peptide for the reasons as set forth with regard to the state of the art and predictability of the scope of the claimed invention. With regard to protein H peptide the specification does not enable the scope of the claimed invention. As previously stated, the state of the art with regard to vaccine compositions against GAS is unpredictable (see above) and the pending specification does not fully enable the scope of the claimed invention such that one of skill in the art would readily be able to make and use the claimed invention (vaccine compositions and methods) without undue experimentation.

5. Claims 3, 8, 9, 14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Lowell et al (Technological Advances in Vaccine Development, 1988, pp 423-432).

Lowell et al discloses isolated meningococcal outer membrane proteins naturally form whole or fragmented hydrophobic membrane vesicles called proteosomes (abstract). Lowell et al discloses that proteosome vaccines can comprise streptococcal M proteins (abstract; p. 430). The prior art discloses that the proteosomes are safe in people and they are simple to produce (abstract). "The proteosome vaccine system we have developed addresses these problems by using components that are safe for human use and unidirectionally binding peptides to proteins via hydrophobic foot (Hft) that is distant from the epitope. Lowell et al discloses a method of immunizing a subject or individual with the proteosome vaccine system comprising the streptococcal M protein (methods, p. 425).

The prior art anticipates the claimed invention. Since the Patent Office does not have the facilities for examining and comparing applicants' vaccines and methods with the vaccines and methods of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed vaccines and methods and the vaccines and methods of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

This rejection is maintained for the reasons of record. Applicant's arguments filed March 9, 2006 have been fully considered but they are not persuasive. Applicants have asserted that Lowell et al does not teach or suggest the claimed invention and that Lowell et al does not teach or suggest that the antigenic peptide may further comprise flanking amino acid sequences that maintain the helical folding of the antigen. It is noted that this aspect in not set forth in the claimed invention (claims 3, 8, 9, 14 and 16). It is also noted that the claims do not recite "a spacer peptide comprising at least two glycine residues, wherein the spacer peptide links the antigenic peptide with the hydrophobic moiety." It is also noted that Lowell et al discloses "...proteosome-enhanced immunogenicity, however, was only evident when the HFt vas at the NH2 terminus. While this does not imply that all peptides need to be linked to proteosomes at their -NH2 terminus, it does indicate that changing linkage orientation can have profound affects on immunogenicity. Peptide length was also important for type 6 immunogenicity since C-SM24-6 vas superior to C-SM6." (p. 430)

6. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowell et al (Technological Advances in Vaccine Development, 1988, pp 423-432) as applied to claims 1-3, 8, 9, 11, 14 and 16 above, and further in view of Brandt et al (Nature Medicine, 2000, 6/4:455-459).

Lowell et al discloses isolated meningococcal outer membrane proteins naturally form whole or fragmented hydrophobic membrane vesicles called proteosomes (abstract). Lowell et al discloses that proteosome vaccines can comprise streptococcal M proteins (abstract; p. 430). The prior art discloses that the proteosomes are safe in people and they are simple to produce (abstract). "The proteosome vaccine system we have developed addresses these problems by using components that are safe for human use and unidirectionally binding peptides to proteins via hydrophobic foot (Hft) that is distant from the epitope. Lowell et al discloses a method of immunizing a subject or individual with the proteosome vaccine system comprising the streptococcal M protein (methods, p. 425). Lowell et al discloses the claimed invention except for the claimed amino acid sequence of M protein.

However, Brandt et al teaches preparing a GAS vaccine comprising the portions of the M protein of GAS (abstract). Brandt et al teaches a region of the M protein in identical in 70% of GAS, and that the optimal candidate might consist of the conserved determinant with common N-terminal sequences found in communities with endemic GAS (abstract; Table 1; p. 458, col. 2). Brandt et al teaches the J14 protein which has the amino acid sequence as set forth in SEQ ID NO: 1 and 2 (see methods, p. 458, col. 2). Brandt et al teaches the use of "...highly effective N-terminal epitopes derived from GAS isolates common to a highly endemic region. Because a vaccine with only N-terminal epitopes would

still be unable to target all GAS endemic to this region, we included a conserved region epitope, J14, to form the basis of a broad-spectrum vaccine. Such a vaccine might be widely effective, but within a high endemic area would be designed to deliver increased protection by targeting both serotypic and conserved determinants on the M protein." (pp. 457-458) Brandt et al teaches the use of carriers or adjuvants in the vaccine composition such tetanus toxoid, diphtheria toxoid, CFA, or alum (p. 456, col. 1; p. 458, col. 2). Brandt et al teaches that compositions comprising J14 and CFA protected 16 of 19 mice against GAS challenge and mice immunized with the composition, comprising J14 and PBS, protected 3 of 15 mice (p. 456, col. 1). Further, 8 of 10 mice vaccinated with the J8 peptide linked to diphtheria toxoid and administered with alum survived GAS challenge (p. 456, col. 1).

Lowell et al teaches that small peptides, "...representing protective epitopes of infectious organisms offer great vaccine potential. Peptide vaccine development, however, has been impeded by the insufficient immunogenicity of peptides given without protein carriers and adjuvants. There is currently a paucity of carriers and adjuvants that are safe for human use. Furthermore, it is frequently difficult to covalently conjugate peptides to protein carriers without obscuring or altering the epitope. Moreover, peptide conjugation to routinely used carriers like tetanus toxoid can result in epitope suppression of peptide immunity. The proteosome vaccine system we have developed addresses these problems by using components that are safe for human use and by unidirectionally binding peptides to proteins via a hydrophobic foot (HFt) that is distant from the epitope." (p. 424)

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Lowell et al and Brandt et al

since both Lowell et al and Brandt et al teach preparing a vaccine to treat GAS for human use and Lowell et al teaches the need for adjuvants, other than alum, for human use. Brandt et al teaches the use of adjuvants or carriers such as tetanus toxoid or diphtheria toxoid. However, in view of the teachings of Lowell et al that peptide conjugation to routinely used carriers like tetanus toxoid can result in epitope suppression of peptide immunity and that a new adjuvant for human use is needed, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the known M protein of GAS as antigen of Brandt et al and the proteosome of Lowell et al in a vaccine composition for human use. The claimed invention is prima facie obvious in view of the combined teachings of the prior art, absent any convincing evidence to the contrary.

7. Claims 10 and 13-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowell et al (Technological Advances in Vaccine Development, 1988, pp 423-432) and Brandt et al (Nature Medicine, 2000, 6/4:455-459) as applied to claims 1-6, 8, 9, 11, 14 and 16 above, and further in view of Relf et al (Advances in Exptal. Med. And Biol., 1997, 418(Streptococci and the Host):859-861.

Lowell et al discloses isolated meningococcal outer membrane proteins naturally form whole or fragmented hydrophobic membrane vesicles called proteosomes (abstract). Lowell et al discloses that proteosome vaccines can comprise streptococcal M proteins (abstract; p. 430). The prior art discloses that the proteosomes are safe in people and they are simple to produce (abstract). "The proteosome vaccine system we have developed addresses these problems by

using components that are safe for human use and unidirectionally binding peptides to proteins via hydrophobic foot (Hft) that is distant from the epitope. Lowell et al discloses a method of immunizing a subject or individual with the proteosome vaccine system comprising the streptococcal M protein (methods, p. 425).

Brandt et al teaches preparing a GAS vaccine comprising the portions of the M protein of GAS (abstract). Brandt et al teaches a region of the M protein in identical in 70% of GAS, and that the optimal candidate might consist of the conserved determinant with common N-terminal sequences found in communities with endemic GAS (abstract; Table 1; p. 458, col. 2). Brandt et al teaches the J14 protein which has the amino acid sequence as set forth in SEQ ID NO: 1 and 2 (see methods, p. 458, col. 2). Brandt et al teaches the use of "...highly effective N-terminal epitopes derived from GAS isolates common to a highly endemic region. Because a vaccine with only N-terminal epitopes would still be unable to target all GAS endemic to this region, we included a conserved region epitope, J14, to form the basis of a broad-spectrum vaccine. Such a vaccine might be widely effective, but within a high endemic area would be designed to deliver increased protection by targeting both serotypic and conserved determinants on the M protein." (pp. 457-458) Brandt et al teaches the use of carriers or adjuvants in the vaccine composition such tetanus toxoid, diphtheria toxoid, CFA, or alum (p. 456, col. 1; p. 458, col. 2). Brandt et al teaches that compositions comprising J14 and CFA protected 16 of 19 mice against GAS challenge and mice immunized with the composition, comprising J14 and PBS, protected 3 of 15 mice (p. 456, col. 1). Further, 8 of 10 mice vaccinated with the J8 peptide linked to diphtheria toxoid and administered with alum survived GAS challenge (p. 456, col. 1).

Lowell et al teaches that small peptides, "...representing protective epitopes of infectious organisms offer great vaccine potential. Peptide vaccine development, however, has been impeded by the insufficient immunogenicity of peptides given without protein carriers and adjuvants. There is currently a paucity of carriers and adjuvants that are safe for human use. Furthermore, it is frequently difficult to covalently conjugate peptides to protein carriers without obscuring or altering the epitope. Moreover, peptide conjugation to routinely used carriers like tetanus toxoid can result in epitope suppression of peptide immunity. The proteosome vaccine system we have developed addresses these problems by using components that are safe for human use and by unidirectionally binding peptides to proteins via a hydrophobic foot (HFt) that is distant from the epitope." (p. 424) Lowell et al and Brandt et al teach the claimed invention except for intranasal administration and prevention or reduction of bacterial colonization of the throat.

However, Relf et al teaches intranasal immunization of mice and the vaccine administered was a GAS based vaccine (title; introduction, p. 859). Relf et al teaches that "...type-specific immunity to GAS infection is long lasting and Abs to the conserved region of M protein increase with age and immune status." (p. 859) "Mucosal immunization has the advantage of inducing immune responses effective at preventing attachment/colonization in the throat (a site of natural infection), and then triggering systemic immunity important for eliminating any invading bacteria." (p. 859) Relf et al teaches the use of various adjuvants (materials and methods, p. 860). Relf et al teaches the production of a serum IgG response as well as IgA and serum IgA (p. 860), which would be indicative of a serum immune response and a mucosal immune response.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of Lowell et al, Brandt et al and Relf et al, since all three references teach preparing a vaccine to treat GAS for human use and Lowell et al teaches the need for adjuvants, other than alum, for human use. Brandt et al and Relf et al teach the use of adjuvants or carriers such as tetanus toxoid or diphtheria toxoid. However, in view of the teachings of Lowell et al that peptide conjugation to routinely used carriers like tetanus toxoid can result in epitope suppression of peptide immunity and that a new adjuvant for human use is needed, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the known M protein of GAS as antigen of Brandt et al and Relf et al and the proteosome of Lowell et al in a vaccine composition for human use. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer the GAS vaccine intranasally since Relf et al teach intranasal immunization with conserved peptides (GAS M protein) linked to cholera toxin subunit B resulted in a significant reduction in pharyngeal colonization of mice following homologous and heterologous GAS challenge. Relf et also teaches that "Mucosal immunization has the advantage of inducing immune responses effective at preventing attachment/colonization in the throat (a site of natural infection), and then triggering systemic immunity important for eliminating any invading bacteria." (p. 859) It would have been obvious to a person of ordinary skill in the art at the time the invention was made to administer the GAS vaccine to an individual, human, since humans are mainly affected by GAS infection. The claimed invention is prima facie obvious in view of the combined teachings of the prior art, absent any convincing evidence to the contrary.

8. With regard to the 103 obviousness rejections set forth in paragraphs 6 and 7 of this Office Action, these rejections have been maintained for the reasons of record. Applicant's arguments filed March 9, 2006 have been fully considered but they are not persuasive. Applicants have asserted that the combination of prior art references does not teach or suggest the claimed invention and that the Examiner has used impermissible hindsight using the teachings in the present specification to assert that an ordinarily skilled person would expect to achieve successfully the claimed vaccine compositions and methods. However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants have asserted that the cited documents do not teach the claimed invention and that Examiner acknowledges that Lowell et al does not teach or suggest a vaccine composition where the antigen comprises an antigenic peptide between 6 and 25 amino acids in length from the conserved C-terminal region of a GAS M protein. However, the Examiner specifically stated that Lowell et al does not teach the specific amino acid sequences set forth in claimed sequences set forth in SEQ ID NO: 1 and 2. Further, with regard to C- or N-terminal, it is noted that Lowell et al discloses "...proteosome-enhanced immunogenicity, however, was only evident when the HFt vas at the NH2 terminus. While this does not imply that all peptides need to be linked to proteosomes at their -NH2 terminus, it does

indicate that changing linkage orientation can have profound affects on immunogenicity. Peptide length was also important for type 6 immunogenicity since C-SM24-6 vas superior to C-SM6." (p. 430) The claimed invention is prima facie obvious in view of the combined teachings in the prior art, absent any convincing evidence to the contrary.

9. No claims are allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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